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PRINCIPAL INVESTIGATOR: Mary Ann Kosir, M.D.

CONTRACTING ORGANIZATION: Wayne State University
Detroit, MI 48202

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Mary Ann Kosir, M.D.

E-mail: ad3208@wayne.edu

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13. SUPPLEMENTARY NOTES

14. ABSTRACT The **purpose** is to evaluate perioperative training for lymphedema assessment and protection. The **hypothesis** is that structured perioperative training in lymphedema protection will decrease lymphedema, the episodes of infection, the time to detection of lymphedema and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group. The **specific questions (scope)** are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group? 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group? **Major Findings:** The incidence of lymphedema was 58.3% with a majority occurring within the first year after surgery. Teaching LE protection methods did not reduce the incidence of LE nor improve QOL. Those with LE had increased knowledge of LE protection methods as compared to a control group despite intense training. **Significance:** The lymphedema rate is greater than reported in the literature primarily because prospective measurements were obtained including the first year after surgery when a majority of cases were observed. Other factors that may impact the occurrence of LE without regard to knowledge of protection measures include impaired lymphatic healing after surgery, persistence of activity despite knowing it may cause harm to the extremity, and uncontrolled hypertension which may increase the risk for LE. These other factors on this significant problem are now the subject of new grant funding.

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Lymphedema, quality of life, education

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INTRODUCTION

Narrative:

Subject: Increasing numbers of breast cancer survivors are at risk for long-term sequelae from treatment. Axillary surgery or radiation therapy to the breast may alter lymph channels, leaving the survivor with a lifetime risk for developing lymphedema. Lymphedema is a swelling of the upper extremity, which causes pain, debility, and reduced quality of life (QOL) that impacts choices about work, social and sexual interactions and self-esteem. Protective measures to reduce the risk of lymphedema become important life-long skills. However, there is inconsistent teaching of protective measures and inattention to lymphedema detection in clinical practice.
Purpose: The purpose of this study is to test that structured perioperative training in lymphedema protection will decrease lymphedema, the episodes of infection, the time to detection of lymphedema and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group.
Scope: The specific aims are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group? 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group?
Methods: Patients with resectable breast cancer also undergoing axillary lymph node surgery and/or radiation therapy to the breast will be prospectively randomized to two groups. In addition to receiving standard care (i.e., written breast rehabilitation materials and preoperative counseling by the breast surgeon), patients in Group 1, will receive structured education in Breast Surgery Rehabilitation including range of motion exercises, lymphedema arm precautions, and management of complications. Patients in Group 2 will receive standard care (written material and preoperative counseling by the surgeon). For both groups, preoperative and then quarterly volume measurements and exams of the upper extremities will be done for three years after surgery in order to determine lymphedema and infection incidence. The QOL will be measured longitudinally by the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the Medical Outcome Study Short Form Health Survey (MOS SF-36) and sexuality subscales of Cancer Rehabilitation Evaluation System (CARES). The knowledge of and practice of lymphedema protective skills will be measured by periodic testing longitudinally as well.

BODY

Components	
1	**Response to Reviewer's comments from previous report**
2	**Research Accomplishments associated with each task in Statement of Work**
3	**Table and Figures corresponding to Specific Aims (Supporting Data)**
4	**Bibliography –Publications and Meeting Abstracts**
5	**List of Personnel receiving pay from the research effort**

Part 1: **Response to Reviewer's comments from Year IV report:**
There were no issues to address. The report was accepted and there were no technical issues.

Part 2: **Research accomplishments associated with each task outlined in the approved Statement of Work. Therefore, the Year V report is cumulative through 8/5/05**
(Tables and Figures are clustered after Statement of Work summary)

Task 1. **Start-up, Months 1-2.**
This was completely accomplished in 2000.

Task 2. **Introduce study to physicians, nurses and clerks in clinics, Months 1-2.**
This was completely accomplished in 2000.

Task 3. **Subject recruitment and data collection, Months 3-60.**
This was completely accomplished.

For the determination of LE and infection rates (Specific Aim 1) in this clinical trial of perioperative education, we report on 163 evaluable participants which meets the goal of at least 158-179 evaluable participants. The analyses of changes in quality of life (QOL) (Specific Aim 2) and determination of knowledge and compliance with LE protection measures (Specific Aim 3) are also based upon this study population.

Task 4. **Perioperative teaching sessions, Months 3-27.**
This was completely accomplished for all participants in the intervention group. Annual Report IV(Appendix Item #1) from last year showed compliance with this item and will not be repeated in this report.

Body Part 2 Research Accomplishments associated with each task in Statement of Work (continued)

Task 5. **Quarterly measurements of subjects, Months 6-60.**

A majority of subjects have completed the 3 year followup. Some require a few more measurements which will be accomplished through a no-cost extension approved through 8/06. From last year's report (Appendix Item #3), we showed the measurement data in centimeters at multiple standardized sites along both upper extremities. If a patient was unable to complete a quarterly measurement, we saw them at the next opportunity.

Task 6. **QOL questionnaires at 6 months, 1-, 2-, and 3-years postop, Months 9-60.**

A majority of subjects have completed the 3-year followup QOL questionnaires.

Task 7. **Booster training session for Group 1 subjects, Months 9-33.**

This was completed for all participants in the intervention group. The list was supplied last year (Appendix Item # 2) and will not be duplicated this year.

Task 8. **Knowledge and compliance questionnaires, Months 9-60.**

A majority of subjects have completed the 3-year followup Knowledge and Compliance questionnaires.

Task 9. **Calculations of limb volumes and comparison of differences, Months 3-60.**

A majority of subjects have completed the 3-year followup.

Weekly report sheets are created and reviewed which show cumulative data:

a) volume changes
b) >1cm measurement changes
c) symptoms

All subjects with >10% volume change, >1cm measurement change and/or persistent symptoms are evaluated by the LE study nurse. An example of the weekly volume report was supplied last year (Appendix Item # 4) and will not be duplicated this year.

Task 10. **Quarterly data entry and print out by the Psychosocial and Behavioral Core, Months 3-60.**

From the previous annual reports, the Psychosocial and Behavioral Core was dissolved by the reorganization at the Karmanos Cancer Institute. Data entry was performed at least weekly by a data manager through 7/7/05. Backup computer discs were made weekly.

Task 11. **Interim analysis of data after 1 year, 3 years, Months 14-16, 38-40.**

This was accomplished, with the most recent analysis after the 4th year instead of the 3rd year due to the power outage in the SE Michigan area in August, 2003. We were excused from this item for the Year III report.

The data tables and figures found in **Part 3 of the Body Section** after this section on Statement of Work were performed with the study statistician. The comparisons of various patient characteristics between the control and intervention arm or between patients with and without lymphedema were performed using 2-sample t-tests and chi-square tests. A multivariable logistic regression with a backward variable selection procedure was also utilized to determine the relationship between lymphedema and various risk factors.

Body Part 2 Research Accomplishments associated with each task in Statement of Work (continued)

Task 12. **Analysis of data after 5th year, Months 61-65.**
Not yet applicable. This will be accomplished with a no-cost extension already approved for months 61-72 instead. Analysis of data for the Annual Report V was performed. Supporting data are found in Part 3 (below) of the Body section. Comments/Discussion appear throughout.

Task 13. **Annual report to USAMRMC, Months to be designated by USAMRMC.**
Completed for each year (I-V).

Task 14. **Meeting in Baltimore, Maryland to disseminate results of DoD-sponsored Research during the second year, Month to be announced by USAMRMC.**
Completed. PI attended September, 2003, Orlando, FL. Poster presentation.

Task 15. **Write journal articles. Submit abstract, Months 12-60+**
Ongoing. Please see Bibliography section (**Part 5 of the Body section**).

Part 3 Tables and Figures (Supporting Data)

Table 1 Population Characteristics of Study Participants

	Intervention Group	Control Group	Univariate
N	78	85	
Mean age, yrs ± S.D.	54.02±11.67	52.86±13.29	P=0.5559
Race			
African American	33.00	35.00	P=1.000 For AA Vs Non-AA
Caucasian	38.00	39.00	
Hispanic	1.00	2.00	
Arab/Chaldean	1.00	2.00	
Asian	0.00	4.00	
Native American	2.00	1.00	
Other	3.00	2.00	
Employment status			P=0.7472 For working vs. other
Working	31.00	31.00	
Not working	21.00	19.00	
Retired	14.00	12.00	
Not answered	12.00	23.00	
Highest education level			P=0.7235 For College Vs. Non-college
Less than high school	2.00	2.00	
Some high school	8.00	6.00	
High school/GED	40.00	42.00	
Bachelor degree	14.00	15.00	
Masters degree	4.00	8.00	
Doctorate/professional school	3.00	1.00	
Not answered	7.00	11.00	
Annual income			P=0.4585 For < $50,000 vs. ≥ $50,000
< $5,000	6.00	8.00	
$5,000-$15,000	9.00	13.00	
$15,001-$30,000	9.00	10.00	
$30,001-$50,000	8.00	8.00	
$50,001-$75,000	9.00	8.00	
> $75,001	17.00	15.00	
Not answered	20.00	23.00	
Marital Status			P=0.4139 For Married/ Cohabitating Vs. All others
Divorced/separated	17.00	14.00	
Married/Cohabitating	38.00	33.00	
Never married	10.00	12.00	
Widowed	9.00	16.00	
Not answered	4.00	10.00	
Transportation			P=0.8700 For Drive myself Vs. All others
Usually drive myself	50.00	56.00	
Usually use public transportation	8.00	2.00	
Usually driven by someone else	15.00	15.00	
Other	0.00	2.00	
Not answered	5.00	10.00	
Religious Preference			P=0.5021 For Christian Vs. Non-Christian
Catholic	21.00	18.00	
Hindu	0.00	1.00	
Jewish	2.00	0.00	
Muslim	1.00	1.00	
Protestant	20.00	20.00	
Other	22.00	30.00	
None	3.00	4.00	
Not answered	9.00	11.00	

Table 2 Clinical Characteristics of Study Participants in the Intervention and Control Groups for LE Protection teaching.

	Intervention Group	Control Group	Univariate
N	78	85	
Breast Cancer Stage			P=1.000 For Stage 0,I vs. Stage IIA,IIB,IIIA,IIIB
0	10.00	8.00	
I	23.00	29.00	
IIA	19.00	19.00	
IIB	14.00	16.00	
IIIA	7.00	8.00	
IIIB	5.00	5.00	
IV	0.00	0.00	
Type of breast and axillary surgery			P=0.3742
Mastectomy + axillary surgery	40.00	51.00	
Lumpectomy + axillary surgery	33.00	27.00	
Lumpectomy	5.00	7.00	
Radiation therapy			P=0.2442
Yes	56.00	53.00	
No	22.00	32.00	
Number of LNs submitted (mean ± SD)	8.64±6.03	9.63±6.23	P=0.3058
≤ 8 LNs submitted	40(51%)	40(47%)	P=0.6395
> 8 LNs submitted	38(49%)	45(53%)	
Number of LNs positive for ca			
0	45(58%)	48(56%)	P=0.6038
1-3	25(32%)	24(28%)	
>4	8(10%)	13(15%)	
Body Mass Index (BMI) (mean ± SD)	29.08±7.12	28.91±7.54	P=0.8882
BMI >25	53(68%)	58(68%)	P=1.000
BMI >30	27(35%)	33(39%)	P=0.6275

Discussion: **Tables I and II** show that the population and clinical characteristics of the study patients for the intervention and control groups show no difference by univariate analysis as expected. This supports the randomization scheme used in the study. Therefore, any differences in LE rate, infection, time to LE are due to other reasons.

Table 3A Incidence of LE in the intervention and control groups (Specific Aim 1)

	Secondary LE (n=95)	Without LE (n=68)	
Intervention (n=78)	50 (64%)	28 (36%)	P=0.1566
Control group (n=85)	45 (53%)	40 (47%)	

Table 3B Incidence of LE in the intervention and control groups (Specific Aim 1) (where ARM LE+ determined by >10% volume increase and confirmed by nurse)

	Secondary LE (n=42)	Without LE (n=121)	
Intervention (n=78)	21 (27%)	57 (73%)	P=0.8580
Control group (n=85)	21 (25%)	64 (75%)	

Table 4 Infection rate in the intervention and control groups, and in those with LE and without LE (Specific Aim 1)

	Infection	No infection	
Intervention (n=78)	4 (5%)	74 (95%)	P=0.7106
Control group (n=85)	3 (4%)	82 (96%)	
LE (n=95)	6 (6%)	89 (94%)	P=0.2406
No LE (n=68)	1 (1%)	67 (99%)	

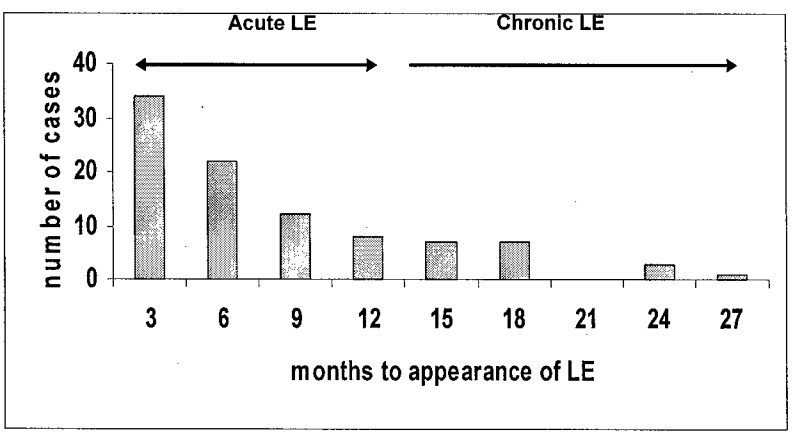

Fig. 1. Determining when secondary LE occurs after breast cancer surgery. Using quarterly prospective upper extremity measurements after breast cancer surgery, determination of secondary LE was made by comparing volume changes to preoperative measurements. These were verified by a LE nurse specialist. The months to appearance of secondary LE are along the x-axis, and number of cases along the y-axis. By definition, acute LE presents and resolves within 12 months. Chronic LE presents after 12 months, or, if acute LE persists after 12 months, it is then considered chronic.

Specific Aim 1: *What is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group?*

Discussion: From Table 3A, the of LE in the intervention group is not significantly different from the control group. The initial determination of LE proposed was a greater than 10% volume increase in the extremity as compared to preoperative baseline volume. Since the study began, we have identified additional criteria that are used in practice, including a greater than 1 cm increase in circumference at any measurement site as compared to baseline and as compared to the contralateral extremity. (Published comparison of methods in J Surg Res 2003; please see Part 4 of Body section and Appendix). Table 3B shows the incidence of LE when the criterion of Greater than 10% volume increase is used. There is still no difference between the intervention Group and the control group. From Table 4, the interim infection rate is similar in the

intervention and the control group. However, there are more subjects with infection in the LE group than in the group without LE. This still does not become significant (P=0.2406). Figure 1 depicts the time to appearance of LE. The majority occur within the first year after surgery. Most persist. Only a minority first occur after the first year of surgery. The time to LE was not different for those in the intervention group or control group. An early paper from this study (J Surg Res 2001; See Part 4 of Body section and Appendix) discussed the appearance of LE within the first year after surgery as well as symptoms preceeding measurement changes by 3 months. The pattern of LE appearance after breast cancer surgery will be presented this Fall, 2005, at the American College of Surgeons. The plan is to perform subset analysis during the next few months looking at the influence of race, age, stage, type of surgery, number of lymph nodes removed and how many positive for cancer, and radiation therapy while examining LE cases as acute, chronic or acute becoming chronic (persistent).

Funding for two sister grants was obtained (2005) to examine influences on the development of LE that exclude teaching. These factors are: inherited polymorphisms in genes that code for lymphatic healing, activities which exacerbate the altered lymphatics postoperatively, and uncontrolled hypertension. A paper has been submitted examining the relationship between uncontrolled hypertension and the development of LE (please see Part 4 of Body section and Appendix).

Table 5 Population Characteristics of Breast Cancer Survivors with and without Upper Extremity Secondary Lymphedema (LE) (Specific Aim 1)

	With LE	Without LE	Univariate
N			
Mean age, yrs±SD(range)	53.78±11.72	52.91±13.63	P=0.5559
Race			P=1.000 For AA Vs Non-AA
African American	39	29	
Caucasian	43	34	
Hispanic	4	0	
Arab/Chaldean	3	0	
Asian	1	3	
Native American	1	2	
Other	4	0	
Employment status			P=0.7448 For working vs. other
Working	36	26	
Not working	21	19	
Retired	18	8	
Not answered	20	15	
Highest education level			P=0.3660 for College Vs. Non-College
Less than high school	11	7	
High school/GED	49	33	
Associate degree			
Bachelor degree	17	12	
Masters degree	6	6	
Doctorate/professional school	2	2	
Not answered	10	8	
Annual income			P=0.8515 for < $50,000 Vs. ≥ $50,000
< $5,000	7	7	
$5,000-$15,000	12	10	
$15,001-$30,000	11	8	
$30,001-$50,000	10	6	
$50,001-$75,000	13	4	
> $75,001	18	14	
Not answered	24	19	
Marital Status			P=0.6219 For Married/ Cohabitating Vs. others
Divorced/separated	19	12	
Married/Cohabitating	44	27	
Never married	14	8	
Widowed	12	13	
Not answered	6	8	
Transportation			P=0.5071 for Drive myself Vs. All others
Usually drive myself	60	46	
Usually use public transportation	8	2	
Usually driven by someone else	20	10	
Other	0	2	
Not answered	7	8	
Religious Preference			P=0.2363 For Christian Vs. Non-Christian
Catholic	25	14	
Hindu	0	1	
Jewish	0	2	
Muslim	2	0	
Protestant	26	14	
Other	28	24	
None	2	5	
Not answered	12	8	

Table 6 Clinical Characteristics of Breast Cancer Survivors with and without Secondary LE

	With LE	Without LE	Univariate
N			
Breast Cancer Stage			P=0.0162
0	5	13	
I	29	23	For Stage 0,I vs. Stage IIA,IIB,IIIA,IIIB
IIA	23	15	
IIB	22	8	
IIIA	9	6	
IIIB	7	3	
IV			
Type of breast and axillary surgery			P=0.1571
Mastectomy with axillary surgery	53	38	
Lumpectomy with axillary surgery	38	22	
Lumpectomy	4	8	
Radiation therapy			P=1.0000
Yes	63	46	
No	32	22	
Number of LNs submitted (mean ± SD)	11.00±5.82	6.57±5.65	
≤ 8 LNs submitted	32 (34%)	48 (71%)	P<0.000004
> 8 LNs submitted	63 (66%)	20 (29%)	
Number of LNs positive for ca			
0	47 (49%)	46 (68%)	P=0.0526
1-3	35 (37%)	14 (21%)	
>4	13 (14%)	8 (12%)	
Body Mass Index (BMI) (mean ± SD)	29.62±7.20	28.13±7.46	P=0.2048
BMI >25	67 (71%)	44 (65%)	P=0.4964
BMI >30	36 (38%)	24 (35%)	P=0.7453

Discussion: From Tables 5 and 6, univariate analysis of those with LE compared with those without LE showed that LE was significantly associated with certain clinical characteristics. These included the number of mean number of lymph nodes resected at surgery especially if >8 lymph nodes were submitted (P<0.000004). Furthermore, while the mean number of lymph nodes positive for metastatic cancer was associated with increased risk for LE, (p=0.0526). There was also increased risk of LE with higher stage of breast cancer (Stage IIA and above vs Stage 0 or I, p=0.0162). There were no population characteristics associated with those with increased risk of LE.

Table 7 The LOGISTIC Procedure -Analysis of Maximum Likelihood Estimates

Model: Lymphedema = Control arm Ln submitted Ln positive Mastectomy Christian

Parameter	Wald Pr > ChiSq	Odds Ratio	95% Wald Confidence Limits	
Intercept	0.1202			
Control arm	0.0965	0.528	0.249	1.121
Ln submitted (>8)	<.0001	5.509	2.474	12.267
Ln positive (>0)	0.0527	2.164	0.991	4.724
Mastectomy (vs. other)	0.2630	0.634	0.285	1.408
Christian	0.0647	2.043	0.957	4.358

Discussion: To investigate whether there are any variables more strongly associated with LE, multivariate analysis was performed. For multivariate analysis, stepwise logistic regression using the backward selection method was performed to determine association with LE by variables in the clinical or population characteristics. LE (yes/no) was dependent, and the other variables were explanatory variables. From Table 7, the highest correlation with developing LE was with any lymph nodes positive ($p=0.0527$) or the number of lymph nodes removed at surgery (<0.001). Being in the control arm did not correlate with higher LE (or being in the intervention arm did not correlate with lower risk for LE). In Table 6 and Table 7, the population and clinical characteristics of subjects with LE are compared with those of subjects without LE. There were no population differences between those with or without LE. However, an additional clinical difference was the stage of breast cancer. As expected, those with LE had a higher stage of breast cancer than those who did not develop LE.

Table 8 **Quality of life (QOL) scores comparing the Intervention Group with the Control Group and those with and without LE (FACT-B, MOS-SF36, CARES marital and sexuality subscales)(Specific Aim 2)**

	Intervention group	Control group	With LE	Without LE
FACT-B scores (Total)				
initial mean(n)	123.49 (69)	105.84 (76)	115.88 (81)	112.16 (64)
6-month mean(n)	124.69 (53)	114.61 (48)	118.49 (67)	122.67 (34)
12-month mean(n)	126.71 (40)	115.70 (49)	118.87 (51)	123.03 (38)
24-month mean(n)	126.87 (19)	134.43 (23)	130.49 (25)	131.78 (17)
36-month mean(n)	98.50 (13)	121.36 (20)	109.15 (21)	117.95 (12)
MOS-SF 36 scores				
Physical Scale				
initial mean(n)	45.46 (68)	49.49 (68)	46.68 (79)	48.58 (57)
6-month mean(n)	42.08 (52)	28.78 (47)	36.06 (67)	35.15 (32)
12-month mean(n)	46.91 (44)	44.32 (45)	46.31 (53)	44.55 (36)
24-month mean(n)	45.59 (19)	48.54 (22)	48.84 (23)	45.03 (18)
36-month mean(n)	43.62 (14)	46.49 (19)	44.64 (22)	46.53 (11)
Mental Scale				
initial mean(n)	49.76 (68)	45.37 (68)	48.70 (79)	46.00 (57)
6-month mean(n)	57.29 (52)	86.16 (47)	63.45 (67)	86.79 (32)
12-month mean(n)	48.48 (44)	52.51 (45)	49.34 (53)	52.24 (36)
24-month mean(n)	51.82 (19)	51.60 (22)	53.12 (23)	49.88 (18)
36-month mean(n)	49.67 (14)	50.14 (19)	49.40 (22)	51.02 (11)
CARES				
Sexuality Subscale				
initial mean(n)	46.73 (59)	48.93 (58)	47.88 (64)	47.76 (53)
6-month mean(n)	47.54 (46)	47.83 (40)	48.07 (57)	46.90 (29)
12-month mean(n)	48.32 (31)	48.55 (44)	48.61 (43)	48.25 (32)
24-month mean(n)	47.43 (14)	48.47 (19)	47.55 (20)	48.77 (13)
36-month mean(n)	50.00 (10)	49.13 (15)	51.53 (15)	46.40 (10)
Marital Subscale				
initial mean(n)	48.46 (59)	51.57 (58)	50.02 (64)	49.98 (53)
6-month mean(n)	49.78 (46)	50.20 (40)	50.60 (57)	48.76 (29)
12-month mean(n)	50.94 (31)	51.00 (44)	51.37 (43)	50.44 (32)
24-month mean(n)	49.36 (14)	51.16 (19)	49.75 (20)	51.39 (13)
36-month mean(n)	53.20 (10)	49.93 (14)	53.50 (14)	48.20 (10)

Specific Aim 2: *What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group?*

Discussion: Table 8 combines scores for the intervention group and control group as well as those with LE and those without LE. Although the prospective randomization of participants into intervention and control groups was as expected, it appears as if baseline QOL scores for Fact B are not similar. The reason for this is unclear, and was not a criterion for prospective randomization. Since our collaborator is at another institution, we plan to review these data and specific subset data for each of the QOL instruments during the no-cost extension. The QOL scores need to be interpreted as compared to the interval when LE was diagnosed. The underlying hypothesis is that QOL is worse with LE.

The MOS-SF 36 has comparable scores among the groups, and subscales from the MOS-SF36 may assist in the understanding of FACT-B scores since they overlap in some domains. Neither of these instruments is specific for LE, but asks about function and body image.

Not all subjects are willing to answer the CARES questionnaire asking about marital and sexual relationships. Only those questionnaires where at least 75% of questions were answered

can be included in an analysis. Our collaborators are also away from their home base and will need to be contacted during this no-cost extension to clarify these results.

Table 9 **Knowledge and compliance questionnaire scores comparing both Intervention group with or without LE and Control group with or without LE (Specific Aim 3)**

	Intervention group	Control group	With LE	Without LE
Knowledge Questionnaire				
initial mean(n)	.4005 (73)	.3580 (82)	.4439 (77)	.3152 (81)
6-month mean(n)	.6859 (59)	.6481 (56)	.7272 (69) *	.5780 (46)
12-month mean(n)	.7661 (41)	.7359 (49)	.7729 (50)	.7206 (40)
24-month mean(n)	.8265 (20)	.7749 (23)	.8376 (25)	.7451 (18)
36-month mean(n)	.8193 (14)	.7171 (21)	.8517 (23)	.5784 (12)
Compliance Questionnaire				
6-month mean(n)	3.25 (53)	3.09 (50)	3.26 (63)	3.04 (40)
12-month mean(n)	3.06 (42)	3.00 (50)	3.12 (54)	2.89 (38)
24-month mean(n)	2.96 (19)	3.17 (24)	3.28 (26)	2.77 (17)
36-month mean(n)	2.95 (15)	3.00 (19)	3.12 (23)	2.69 (11)

* Statistically significant at the overall experiment-wise error level of .05 (p-value=0.0024)

Specific Aim 3) *What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group?*

Discussion: As a review, the knowledge questionnaires were given preoperatively and at 6 months, 12 months, 24 months and 36 months after surgery. There are 17 questions that cover several categories of protection methods to reduce the risk of LE. They are scored either 0 or 1 and the Total Score is just the proportion marked 1. The compliance questionnaires are given at the same intervals as the knowledge questionnaires with the exception that no preoperative compliance questionnaire is given. There are 22 questions with each scored from 0 to 4 depending on the frequency of use of a particular protection method. Total Score is the sum of these values divided by the number of questions answered.

Although not significant, it appears as if there were more items answered in the knowledge questionnaire among those in the intervention group as compared to the control group for each interval. However, when comparing those with LE to those without LE, there were significantly more items identified as protection measures in those who had LE as compared to those without LE (p=0.0024). For all intervals, it appears that those with LE score better on the knowledge questionnaire although it is not significant. There may be improvement in the knowledge of LE once a patient has the condition.

Surprisingly, the compliance with protective measures is not greater for those in the intervention group as compared to the control group. In addition to a class with a LE nurse specialist, the intervention group also had a 6 month booster session. It appears that those with LE also show better compliance with protection measures as compared to the control group, but this also is not significant. The collaborator for the Knowledge and Compliance questionnaires will need to be contacted during the no-cost extension to assist in further analysis. They have moved from their former position into a new job.

Part 4 Bibliography

Publications

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Bland, K.L., Perczyk, R., Du, W., Rymal, C., Koppolu, P., McCrary, R. Kosir, MA Can a practicing surgeon detect early lymphedema reliably? Am J Surg., 186:509-513, 2003.

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Meeting Abstracts/Presentations

2000 "Surgical Outcomes after Breast Cancer Surgery: Measuring Acute Lymphedema", 24th Annual Surgical Symposium, Association of VA Surgeons, Seattle, WA. (Accepted abstract; oral presentation)

2002 Lymphedema Prophylaxis Utilizing Perioperative Education. Department of Defense Breast Cancer Research Program Meeting "Era of Hope" , Orlando, FL. (Poster presentation)

Kosir, M.A., Rymal C., Du, W., Koppolu, P., Smith, D., Mood, D., Rice, V., Northouse, L., Aref, A., Brown, M., Youssef, E. Lymphedema Prophylaxis Utilizing Perioperative Education. Department of Defense Breast Cancer Research Program Meeting "Era of Hope" Proceedings III:P58-9, 2002 (Abstract)

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2003 Lymphedema Detection by Circumferential Measurements, 5th Annual Lynn Sage Breast Cancer Symposium, Chicago, IL. (Accepted abstract;poster presentation)

2003 Can a Surgical Practice Detect Lymphedema? 27th Annual Surgical Symposium, Association of VA Surgeons, Nashville, TN. (Accepted abstract; oral presentation).

2004 Equality in Male Breast Cancer Care Using Sentinel Lymph Node Biopsy, 28th Annual Surgical Symposium, Association of VA Surgeons, Richmond, VA. (Accepted abstract; poster presentation).

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2005 Poorly Controlled Hypertension as a Co-Morbid Condition Affection Lymphedema Risk in Breast Cancer Surgical Patients, 29th Annual Surgical Symposium, Association of VA Surgeons, Richmond, VA. (Accepted abstract; oral presentation).

2005 Education, knowledge and behavior change among breast cancer survivors with lymphedema. Society for Applied Anthropolgy, Santa Fe, New Mexico (Accepted abstract; oral presentation).

2005 Clinical Patterns of Lymphedema After Breast Cancer Surgery: When Does It Occur? American College of Surgeons 2005 Clinical Congress, San Francisco, CA (Accepted abstract; Scientific exhibit).

2005Clinical Patterns of Lymphedema After Breast Cancer Surgery: When Does It Occur?, American College of Surgeon 2005 Clinical Congress, San Francisco, CA. (Accepted abstract;Scientific Exhibit).

Part 5 List of Personnel receiving pay by this research effort

Aref, A
Balon, J
Bedoin, J
Brown, M
Darga, L
Du, W
Foley, P
Gonik, N
Hryniuk, L
Jain, V
Kimler, V
King, S
Koppolu, P
Kosir, M
Liguminati, S
Northouse, L
O'Connor, S
Parlapalli, M
Perczyk, R
Rymal, C
Smith, D
St.Onge, K
Wang, W

KEY RESEARCH ACCOMPLISHMENTS

- **A 2001 article was published and presentation made at a national meeting that documented lymphedema within the first year after breast cancer surgery as well as symptoms of LE preceeding measurement changes by 3 months (J Surg Res 95:147-151, 2001).** The article was cited by Dr. Armer and a collaboration formed to standardize the symptom reporting for LE. Two additional presentations at national meetings showed the patterns of LE occurrence from interim data.
- **A 2003 article (Am J Surg., 186:509-513, 2003) was published and presentation made at a national meeting that compared various methods and standards for defining LE in the literature. Using the methods in this study as the "gold standard", the use of a 5% volume or circumference change had a high positive predictive value for identifying LE. This method can be taught to surgical practices so that preoperative measurements can be obtained and postoperative visits can repeat these measurements to simplify identification of those who should be referred to a LE expert.**
- **A 2005 article was submitted and presented at a national meeting that correlated uncontrolled hypertension with development of LE using a prospective measurement collection method, unlike that previously reported in the literature. These findings have been incorporated into a funded study where the influence of blood pressure control on the occurrence of LE is being studied. A manuscript is in press comparing different standards of reporting LE.**

REPORTABLE OUTCOMES

---<u>Manuscripts and presentations</u>
Please see bibliography in **Part 4 of Body** of this report and **Appendix.**

---<u>Funding Applied</u>
Komen Foundation Postdoctoral Fellowship Research Award, "Increased Incidence of Lymphedema in African American and Hispanic Breast Cancer Patients", submitted 8/03, not funded.

$261,251 (PI), WSU Research Enhancement Program, "Looking for Answers in Lymphedema Prevention: Is it what we inherit? Is it what we do? Is it what we treat?", 5/1/05-4/30/07.

$250,000 (PI), Komen Foundation, "Linking Lymphedema to Disorders of Lymphangiogenesis", 5/1/05-4/30/07.

NIH, "Linking Lymphedema to Disorders of Lymphangiogenesis", submitted 6/04, being revised.

CONCLUSIONS

- **Lymphedema was detected in 58.3% of participants who underwent breast cancer surgery using prospective arm circumference measurements and volume determinations for the upper extremities.**
- **The incidence of LE and infection did not differ for those breast cancer patients who received perioperative training in lymphedema protection as compared to a control group (Specific Aim 1). The possibilities: the training needs to be re-formatted, or there are other influences on the development of LE despite knowledge of protection methods (Specific Aim 3). The latter is the basis of two funded grants emanating from this project investigating inherited defects in lymphangiogenesis genes, the effect of activities, and the effect of uncontrolled hypertension.**
- **A majority of LE cases occurred within the first year after breast cancer surgery (78.4%). Furthermore, a majority of cases persisted after the first year.**
- **The quality of life as affected by LE is not measured by FACT-B or MOS-SF 36. This led to the inclusion of qualitative interviews in a funded grant whereby study participants are asked about barriers to compliance with LE protection methods.(Specific Aim 2).**

"So What Section"

There has been resurgence in the interest of lymphedema as evidenced by new funding opportunities for researchers. However, the awareness of lymphedema occurrence, protection, and treatment by many clinicians that are in contact with breast cancer survivors is not uniform. As a result of this research project, this group has had the opportunity to present at national meetings. The latest will be the American College of Surgeons. This is significant because lymphedema is a consequence of treatment for breast cancer, including surgery of the axilla. This provides an excellent forum to discuss findings and possibly influence surgical practice.

REFERENCES

n.a.

APPENDIX

Articles published and submitted included in the appendix:

1. Kosir, M.A., Rymal, C., Koppolu, P., Hryniuk, L., Darga, L., Du, W., Rice, V., Mood, D., Shakoor, S., Wang, W., Bedoyan, J., Aref, A., Biernat, L Northouse, L. Surgical Outcomes after Breast Cancer Surgery: Measuring Acute Lymphedema. J Surg Res 95:147-151, 2001.

2. Bland, K.L., Perczyk, R., Du, W., Rymal, C., Koppolu, P., McCrary, R. Kosir, MA Can a practicing surgeon detect early lymphedema reliably? Am J Surg., 186:509-513, 2003.

SUPPORTING DATA

Please see **Part 3 of Body** of this report for Tables and Figures.

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Surgical Outcomes after Breast Cancer Surgery: Measuring Acute Lymphedema

Mary Ann Kosir, M.D.,*,†,‡,[1] Christine Rymal, M.S.N.,†,§ Prathima Koppolu, M.B.B.S.,‡ Lynn Hryniuk, M.S.N.,† Linda Darga, Ph.D.,‖ Wei Du, Ph.D.,‖,[3] Virginia Rice, Ph.D.,**,†† Darlene Mood, Ph.D.,**,†† Shakeela Shakoor, M.D.,* Wenlian Wang, M.D.,‡ Jirair Bedoyan, Ph.D.,‡ Amr Aref, M.D.,‡‡ Laura Biernat, M.D.,§§,‖‖ and Laurel Northouse, Ph.D.[¶¶]

*Surgical Section, John D. Dingell VA Medical Center, Detroit, Michigan; †Breast Program, Barbara Ann Karmanos Cancer Institute, Detroit, Michigan; ‡Department of Surgery, School of Medicine, Wayne State University, Detroit, Michigan; §Prevention Program, Barbara Ann Karmanos Cancer Institute; ‖Department of Internal Medicine, School of Medicine, Wayne State University; [3]CETAID, Barbara Ann Karmanos Cancer Institute; **Department of Family and Community Nursing, College of Nursing, Wayne State University; ††Psychosocial and Behavioral Oncology Core, Barbara Ann Karmanos Cancer Institute; ‡‡Radiation Oncology, St. John Hospital, Detroit, Michigan; §§Hematology/Oncology, St. John Hospital; ‖‖Ann Arbor Regional Community Cancer Oncology Program (CCOP); and [¶¶]School of Nursing, University of Michigan, Ann Arbor, Michigan

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Background. **Studies of lymphedema have used inconsistent measures and criteria. The purpose of this pilot study was to measure the onset and incidence of acute lymphedema in breast cancer survivors using strict criteria for limb evaluation.**

Materials and Methods. **Eligible women were those undergoing breast cancer surgery that included axillary staging and/or radiation therapy of the breast. Arm volume, strength, and flexibility were measured preoperatively and quarterly. Lymphedema was defined as a greater than 10% increase in limb volume. Additional strength and flexibility assessments were done at these times.**

Results. **In 30 evaluable patients, half underwent modified radical mastectomy and half lumpectomy, with half of the lumpectomy patients undergoing axillary node staging. Of the 30 patients 27% were Stage 0; the rest were Stage I (27%), IIA (13%), IIB (23%), and IIIA (7%). One subject was IIIB postoperatively. There were 2 women with a 10% or greater change in limb volume; the change was detected in one woman at 3 months (5% incidence) and in the second woman at 6 months (11% incidence). Both had undergone mastectomy and axillary dissection and one of these two women had symptoms of tingling and numbness in the affected arm that began at 3 months. Overall, 35% of the sample experienced symptoms by 3 months, which included numbness, aching, and tingling of the entire upper extremity, but without volume changes. The relationship between undergoing modified radical mastectomy and experiencing symptoms in the affected limb at 3 months was significant ($P = 0.05$).**

Conclusions. **In this interim report strict methods of measurement and limb volume comparisons detected acute lymphedema at 3 months in 5% of the sample, and at 6 months in 11% of the sample. Furthermore, symptoms were detected in 35% without volume changes at 3 months postoperatively, which may warn of lymphedema occurrence within the next 3 months. This may assist clinical evaluation of symptoms in the postoperative period and support early referral to lymphedema experts.**

Key Words: **lymphedema; breast cancer; surgical outcomes.**

INTRODUCTION

Breast cancer is a significant cause of morbidity and mortality among women in the United States. It is the second leading cause of cancer-related death and the most commonly diagnosed nondermatologic cancer for this group. In 2000, it is expected that 182,800 women will be diagnosed with breast cancer, and 41,200 will die from the disease [1]. While the incidence of breast cancer has increased over the past two decades, the

Presented at the 24th Annual Symposium of the Association of Veterans Administration Surgeons Meeting, Seattle, Washington, April 9–11, 2000.

[1] To whom correspondence should be addressed at VAMC (11S), 4646 John R, Detroit, MI 48201. Fax: 313-576-1002. E-mail: Mary.kosir@med.va.gov.

0022-4804/00 $35.00

mortality rates began to decrease 1.8% per year between 1990 and 1994 [2]. The increasing incidence rates coupled with declining mortality rates result in increasing numbers of breast cancer survivors.

Lymphedema is a significant concern for breast cancer survivors [3, 4]. Briefly, lymphedema is the result of the accumulation of protein-rich fluid in the tissue after lymphatic channels have been altered [5]. This occurs most directly with axillary lymph node dissection during breast cancer surgery [6, 7]. The resulting swelling in the upper extremity is painful and disfiguring and may lead to loss of function. Other contributors to the development of lymphedema are radiation therapy, obesity, and postoperative infection [6–8].

With increasing numbers of long-term breast cancer survivors at lifelong risk for this disorder, it is expected that lymphedema will be a persistent concern for patients and clinicians alike. From the analysis of several studies, Petrek and Lerner estimated that 16–25.5% of breast cancer patients would develop lymphedema in their lifetime [9]. Studies report a range of 2–24% for the incidence of lymphedema probably due to varying populations, different lengths of follow-up periods, varying techniques of surgery and radiation treatments, and inconsistent techniques for measuring and defining lymphedema [10, 11]. Without a standard for measuring and defining lymphedema, its true incidence cannot be accurately determined. Furthermore, acute lymphedema may occur within the first year after surgery and lead to chronic lymphedema. Therapy may assist resolution of acute lymphedema, thereby avoiding more chronic disability. Therefore, the purpose of this pilot study was to determine the onset and incidence of acute lymphedema in breast cancer patients using a standardized definition and method of detection. The following is an interim report at 6 months.

METHODS

Participants. After approval by the Human Investigation Committee at Wayne State University, 34 patients from the Alexander J. Walt Comprehensive Breast Center of the Karmanos Cancer Institute were enrolled into the study with signed informed consent before surgery. Eligible patients were at least 18 years old with newly diagnosed breast cancer (Stage 0, I, II, IIIA), and scheduled to undergo mastectomy or lumpectomy with lymph node sampling, dissection or sentinel node biopsy, or lumpectomy without axillary staging. Exclusionary criteria included previous ipsilateral axillary radiation, mastectomy alone, could not give consent, or inability to follow-up. The collected data include pathology of the breast cancer and lymph nodes, type of breast and axillary surgery, and stage of the cancer. Quality of life (QOL) was measured perioperatively using the Functional Assessment of Cancer Treatment–Breast (FACT-B), which is a multidimensional QOL tool used frequently in breast cancer studies [12, 13]. The mean FACT-B score for the participants was 113.8 ± 18.1, and will be followed longitudinally.

Measurements. Preoperative weight and measurements of bilateral arm circumferences were obtained. The volume of a series of frustums is considered the most accurate estimate of arm volume

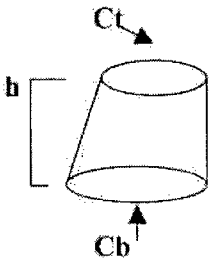

FIG. 1. Volume of a frustum where h = height, Ct = circumference of the top of the frustum, Cb = circumference of the bottom of the frustum: Volume = $h \cdot ((Ct \cdot Ct) + (Ct \cdot Cb) + Cb \cdot Cb)/12 \cdot \pi$.

(Fig. 1). A frustum is a truncated cone with parallel "apex" and base [14, 15]. Circumferential measurements were made of both upper extremities at 10-cm intervals starting at the hand. The volumes for each frustum (segments of the upper extremity) were summed to obtain the total limb volume. Quarterly limb volumes were compared to the preoperative ipsilateral volume. The percentage of volume change was determined as follows: percentage change in limb volume = (current volume − preop volume)/preop volume) × 100. If weight changed by 10 pounds or more from the previous quarter, repeat circumferential measurements were made of both upper limbs and volume was recalculated for a new baseline volume. For this study, the definition of lymphedema was a 10% or greater limb volume increase compared to preoperative limb volume [16]. Evaluation for infection, skin changes, condition of nails, grip strength, and bilateral shoulder range of motion was made, as well as subjective sensations, e.g., tightness, pain, or paresthesia.

Statistical analysis. Standard descriptive statistics were reported on participant characteristics and measures. Univariate comparison using Fisher's Exact test assessed the relationship between subjective symptoms and measured variables. A P value of 0.05 or less was considered significant and all tests were one-sided.

RESULTS

Characteristics of participants. Of 34 women enrolled in the study, there were 30 evaluable, after 4 were removed from the study (3 could not devote time to the study, 1 did not undergo axillary staging or radiation therapy after lumpectomy). The mean age of 51.7 ± 12.0 years. There were 53% Caucasian, 33% African American, 3% Hispanic, and 3% Native American patients (Table 1). Sixty percent were married, 30% divorced or widowed, and 10% single. A majority (85%) were high school graduates with 22% having college degrees. The median income was $30,001–$50,000.

Half (15) underwent mastectomy with axillary dissection, and 15 underwent lumpectomy with postoperative radiation therapy (Table 2). Axillary staging was performed in 7/15 (47%) of lumpectomy patients. Two had sentinel node biopsies with axillary sampling. The other 8 patients with lumpectomy for ductal carcinoma *in situ* did not undergo axillary surgery. Twelve participants (27%) had DCIS (Stage 0) and the rest (22 participants) had invasive breast cancer (Table 3). There were 8 patients with Stage I, 11 with Stage II, and 2 with Stage IIIA. One patient was restaged from

TABLE 1

Demographic Data on Study Participants from the Walt Breast Center, Karmanos Cancer Institute

Characteristic	Frequency (%)
Age (years) (n = 30)	
30–39	6 (20)
40–49	8 (27)
50–59	9 (30)
60–69	4 (13)
70–79	2 (7)
80 and above	1 (3)
A. Race (n = 30)	
African American	10 (33)
Caucasian	16 (53)
Hispanic	1 (3)
Native American	1 (3)
Not answered	2 (7)
B. Marital Status (n = 30)	
Married	18 (60)
Divorced	3 (10)
Widowed	6 (20)
Not married	3 (10)
Education (highest level) (n = 27)	
High school diploma	17 (63)
Bachelors degree	4 (15)
Masters degree	2 (7)
Not answered	4 (15)
C. Employment Status (n = 27)	
Employed	15 (56)
Not employed	6 (22)
Retired	6 (22)
D. Annual Income (n = 27)	
Less than $5,000/year	4 (15)
$5,000–$15,000/year	1 (4)
$15,001–$30,000/year	6 (22)
$30,001–$50,000/year	1 (4)
$50,001–$75,000/year	3 (11)
Greater than $75,000/year	7 (26)
Not answered	4 (15)

stage IIIA to IIIB after surgery. There were no postoperative infections in these patients. One developed chest wall recurrence at 6 months.

Volumetric changes. Initial limb volumes on the affected side ranged from 1407 to 3660 cc, with a mean of 2171 cc (±597 cc). Limb volumes were directly proportional to body mass index. With continuous accrual

TABLE 2

Definitive Breast Cancer Surgery Stage I, II, IIIA (n = 30)

Type of Surgery	Frequency (%)
Modified radical mastectomy	15 (50)
Lumpectomy + planned radiation therapy	15 (50)
With axillary staging	7
Without axillary staging (DCIS)	8

TABLE 3

Breast Cancer Stage in Surgical Participants

Stage (n = 30)	Frequency (%)
0	8 (27)
I	8 (27)
IIA	4 (13)
IIB	7 (23)
IIIA	2 (7)
IIIB*	1 (3)

* Changed from IIIA to IIIB after surgery.

of participants, the compliance with 3-month follow-up was 87% (20/23), and 75% for the 6 month follow-up (9/12).

Two participants developed lymphedema, as determined by a 10% or greater volume increase. One woman had 13.5% change in volume of the affected limb at 3 months (5% incidence). She had undergone lumpectomy with axillary dissection, followed by mastectomy to achieve negative margins. She had Stage IIB disease with three lymph nodes positive for cancer, and had begun chemotherapy within a month of surgery. Her grip strength, shoulder external rotation, and arm extension were equal bilaterally, and she experienced no symptoms. The second woman experienced a 9.9% volume increase at 6 months (11% incidence). She had Stage IIIB disease (restaged from IIIA preoperatively), and had undergone a modified radical mastectomy with five lymph nodes positive for cancer. At 6 months, chest wall metastases were noted, with limb numbness, burning, and itching, and decreased grip strength. She had been symptomatic at 3 months with numbness and pain, but without limb volume change at that time. She had started chemotherapy within a month of surgery.

Seven women (35% incidence) described symptoms at 3 months without volumetric changes in the affected limb, including pain, numbness, dull ache, sharp pain, pins and needles sensation, and throbbing. Two patients experienced decreased grip strength and one showed reduced external rotation and arm extension. Significantly, only those who underwent a modified radical mastectomy experienced symptoms, while those who underwent lumpectomy (with or without axillary dissection) experienced none (P = 0.05) (Table 4). Three of nine participants who reached 6 months follow-up were symptomatic, and one had volumetric changes (Table 4).

DISCUSSION

Even though the standards for measuring and defining lymphedema are not agreed upon, surgical outcomes are being reported. Petrek and Lerner noted

TABLE 4

Relationship between Limb Symptoms and Type of Surgery (Excluding Volumetric Changes)

	Type of surgery	
	Mastectomy and LN	Lumpectomy ± LN
At 3 months		
Symptomatic (n = 7)	7[a]	0[a]
Asymptomatic (n = 13)[b]	5	8
At 6 months		
Symptomatic (n = 3)[c]	1	2
Asymptomatic (n = 6)	2	4

[a] P = 0.05 by Fisher's Exact Test.

[b] One subject had lymphedema by 13.5% volume change without other symptoms.

[c] One subject had lymphedema by 10% volume change and symptoms.

that a reduction in lymphedema did not result from the use of breast conserving surgery, although previously, the incidence declined when the modified radical mastectomy replaced the radical mastectomy as the standard procedure for breast cancer [10]. A recent study reported that 18% of those undergoing breast conservation surgery developed lymphedema within 4 years of treatment [17]. Another reported 3.5% incidence of hand swelling in Stage I and II patients after axillary node dissection [18]. Earlier breast cancer detection may further limit axillary surgery and result in a reduced incidence of lymphedema [19].

The status of axillary lymph nodes in breast cancer is still the basis for treatment decisions [20, 21]. Early detection and treatment have led to the newer approaches to lymph node assessment, axillary sampling, and sentinel node biopsy. In a comparison between axillary sampling and axillary clearance (dissection), the incidence of persistent arm swelling over 4–7.5 years after mastectomy was 20.4% for the node sampling group and 20% for the node clearance group [22, 23]. However, in the axillary sampling group, if lymph nodes were involved with cancer, and subsequent radiation therapy to the axilla was used, the incidence of lymphedema was 32%, compared to 7.7% for those without radiation therapy to the axilla. Sentinel node biopsy assesses the first lymph node(s) draining the breast cancer. The accuracy of axillary evaluation by sentinel node(s) corresponds to that of evaluation by axillary dissection in clinical trails. But issues of the skill level of the surgeon and drainage to areas outside the axilla are subjects of ongoing studies [24, 25]. The impact of sentinel node biopsy on the incidence of lymphedema has not been reported.

By definition, acute lymphedema occurs and resolves within the year following surgery and/or radiation, representing successful adaptation to altered anatomy. Chronic lymphedema can occur at any time after treatment and is irreversible. Therefore, it is important to detect and treat edema of the extremity to resolve acute lymphedema. In this pilot study and interim report, symptoms suggestive of lymphedema were detected in 35% of the sample at 3 months. However, only one subject had a change in limb volume of 13.5% for an incidence of 5% at 3 months. Another asymptomatic subject had a change of limb volume of 8.9%. It will be determined if the limb will further increase in volume during the next quarter. In the nine participants who were also evaluable at 6 months, one was symptomatic and with a volume change of 9.9%. She had some milder symptoms without volumetric changes at 3 months. Two other patients experienced symptoms for the first time at 6 months, but without volumetric changes. So, at 6 months, 3/9 women (33%) were symptomatic with lymphedema in one (11%).

Routine screening for lymphedema within the first 3–6 months postoperatively may reveal symptoms that predict future limb volume changes in breast cancer survivors. These symptoms may be associated with neuropathy, and not lymphedema in some cases. Likewise, volumetric changes that are slight may resolve. This information has not been previously available, and should prove helpful to clinicians who must interpret symptoms and decide on referrals to lymphedema specialists. In addition, the impact of other variables, i.e., nodal status, type of surgery, and other disease features, on the risk for acute lymphedema (and chronic lymphedema) still requires analysis.

Left untreated, chronic lymphedema is a progressive disorder characterized by chronic inflammation, swelling, fibrosis, and increased risk for cellulitis [6]. Physical distress occurs with pain, impaired function of the extremity, and difficulty fitting the bulky limb into clothes [26, 27]. Limitations in shoulder range of motion and grip strength have been documented [27, 28], even in cases of reduced axillary surgery [22, 23]. Psychosocial morbidity is also significant and includes altered body image, feelings of abandonment by medicine, and the burden of chronic therapy [3, 29]. This argues for early detection and prompt referral to lymphedema therapy.

In summary, this pilot study of breast cancer survivors detected acute lymphedema by strict volumetric criteria in 2/30 patients, one at 3 months (5% incidence) and another at 6 months (11% incidence) postoperatively. In addition, 35% experienced symptoms suggestive of lymphedema at 3 months, with one developing a 10% volume change in the affected limb within the next 3 months. The time to detect early changes leading to lymphedema may be in the first 3–6 months after surgery. Routine evaluation of symptoms provides the opportunity for referral to lymphedema experts for treatment, which can minimize chronic

changes. The development of postoperative screening protocols are recommended for early detection of lymphedema. This pilot study supports the performance of a larger study with longer follow-up, utilizing strict measurements and criteria for postoperative lymphedema.

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Excerpta Medica

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Scientific paper

Can a practicing surgeon detect early lymphedema reliably?

Keiva L. Bland, M.D.[a], Rebecca Perczyk, B.A.[a], Wei Du, Ph.D.[b,c], Christine Rymal, M.S.N.[a,d,e], Prathima Koppolu, M.B.B.S.[a], Ruthie McCrary, M.D.[a], Kathryn A. Carolin, M.D.[a,e], Mary Ann Kosir, M.D.[a,e,f,*]

[a]*Department of Surgery, School of Medicine, Wayne State University, Detroit, MI, USA*
[b]*Department of Internal Medicine, School of Medicine, Wayne State University, Detroit, MI, USA*
[c]*CETAID, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA*
[d]*Prevention Program, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA*
[e]*Breast Program, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA*
[f]*Surgical Section, John D. Dingell VA Medical Center (11S), 4646 John R, Detroit, MI 48201, USA*

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Abstract

Background: Lymphedema may be identified by simpler circumference changes as compared with changes in limb volume.
Methods: Ninety breast cancer patients were prospectively enrolled in an academic trial, and seven upper extremity circumferences were measured quarterly for 3 years. A 10% volume increase or greater than 1 cm increase in arm circumference identified lymphedema with verification by a lymphedema specialist. Sensitivity and specificity of several different criteria for detecting lymphedema were compared using the academic trial as the standard.
Results: Thirty-nine cases of lymphedema were identified by the academic trial. Using a 10% increase in circumference at two sites as the criterion, half the lymphedema cases were detected (sensitivity 37%). When using a 10% increase in circumference at any site, 74.4% of cases were detected (sensitivity 49%). Detection by a 5% increase in circumference at any site was 91% sensitive.
Conclusions: An increase of 5% in circumference measurements identified the most potential lymphedema cases compared with an academic trial.

Keywords: Lymphedema; Measurements; Circumference

Halsted described lymphedema of the upper extremity after treatment of breast cancer by mastectomy in the early 1920s [1]. It continues to be of significant lifelong concern even with modern treatment of breast cancer. The incidence of lymphedema has been reported from 6% to 30% [2]. Early and reliable diagnosis continues to be challenging because multiple methods of detection are reported that are difficult to compare. The delay in identification of lymphedema contributes to the negative psychosocial impact already imposed by the potential physical limitations, discomfort, and disfigurement that result from the condition.

There are various methods reported for the detection of lymphedema including water displacement measurement of arm volume, tissue tonometry, and radiographic means such as magnetic resonance imaging (MRI) and computed tomography (CT). However, more commonly, circumferential measurements are used to detect lymphedema. As of yet, however, there are no well-established guidelines for diagnosis of lymphedema using circumferential measurements and no consensus on what measurement change constitutes lymphedema [3]. In a review of the literature by Petrek and Heelan [2], the definition of lymphedema ranged from greater than 2 cm change to greater than 10 cm change. There are reports citing that a greater than 2 cm difference from baseline (preoperative) measurements identifies lymphedema [4,5]. Generally, two or more circumferential measurements are taken along the arm, including at bony landmarks, to evaluate for lymphedema [5,6].

In a prospective trial from the American College of Surgeons Oncology Group (ACOSOG) [7], lymphedema is described as a 2 cm or greater increase over the baseline measurement or greater than 10% increase in circumference

* Corresponding author. Tel.: +1-313-576-3970; fax: +1-313-576-1002.
E-mail address: mary.kosir@med.va.gov

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of the ipsilateral arm. In addition, for the purpose of the ACOSOG protocol, participating members are instructed to take the measurements 10 cm proximal and distal to the lateral epicondyle.

In order to verify and compare various circumference change criteria for lymphedema detection, a group of lymphedema cases were identified by volumetric determinations prospectively collected on breast cancer patients in an academic trial that included examination by a lymphedema specialist. A 10% increase in limb volume was accepted as lymphedema [8,9]. In addition, any change in circumference greater than 1 cm led to examination and measurement by a lymphedema specialist, identifying additional lymphedema cases. Then measurements in the lymphedema cases identified in the academic trial were compared with other definitions of lymphedema that used fewer sites for detection, and various changes in circumference in order to determine specificity and sensitivity of lymphedema detection.

Methods

After approval by the Human Investigation Committee at Wayne State University and human subjects subcommittee of the DoD (DAMD 17-00-1-0495), patients from the Alexander J. Walt Comprehensive Breast Center at Karmanos Cancer Institute were enrolled prior to surgery, and after signing the approved study consent form. Participants were 18 years old or older, male or female, with newly diagnosed, resectable breast cancer. Eligible subjects were scheduled to undergo mastectomy or lumpectomy with lymph node sampling, dissection, or sentinel node biopsy, or breast conservation therapy followed by radiation therapy. Exclusion criteria included previous axillary surgery or radiation, planned mastectomy without axillary surgery or radiation therapy, inability to provide consent, or no plans to follow up at any of the Karmanos facilities after surgery. Demographic information was collected by questionnaire, which included ethnicity, education level, and income. The type of surgery, breast cancer stage, occurrence of chemotherapy and radiation therapy was recorded during the study.

From June 1999 through December 2002, 107 subjects were enrolled and evaluated for lymphedema after surgical treatment of breast cancer. Of 107 subjects, 90 subjects were evaluable. The reasons for nonevaluable subjects were as follows: subjects did not want to continue in the study (10), did not meet study entry criteria upon review (5), or did not undergo axillary surgery or radiation therapy as planned (2). Measurements were taken preoperatively of bilateral arms. The circumferential measurements were taken across the palm of the hand, at the wrist, and at 10 cm intervals proximal to the wrist, and at the elbow. The volume was then calculated based on the total volume of a series of frusta. A frustum, a cone with the top cut off so the upper surface is parallel to the base, is felt to be a more accurate representation of the upper extremity [7,8,10,11]. Measurements and volume calculations were taken quarterly for up to 3 years. Quarterly limb volumes were compared with preoperative values on the ipsilateral side. In the event that a patient had a change in weight of 10 pounds or greater (gain or loss), then measurements were repeated and volumes calculated creating a new baseline. Percent change from preoperative volumes were calculated quarterly using the following equation: volume % change = (current volume − preoperative volume/preoperative volume) × 100 [9]. A 10% increase in volume as compared with preoperative measures was considered to be lymphedema after verification by a lymphedema specialist. In addition, anyone with a circumference measurement increase of greater than 1 cm was also referred to the lymphedema specialist for additional measurements and examination. Not all of these were judged to have lymphedema, but this route identified some additional cases (38.5%).

For comparison, the criterion of a 10% change and 5% change in circumferential measurement was applied to the sites proximal and distal to the elbow. This was done to evaluate the effectiveness of the two-site method to diagnose lymphedema as compared with the sites measured for the academic trial. Then 10% change and a 5% change in circumference at any of the measured sites along the limb were calculated. Additionally, measures greater than 2 cm were also identified. The lymphedema specialist evaluated all potential cases of lymphedema identified by these comparison methods in order to determine true positive and true negative cases. The time of diagnosis of lymphedema was determined as months after the date of surgery. The sensitivity and specificity of each of the methods using circumference changes were determined in comparison to the lymphedema cases confirmed in the academic trial. The timing of the diagnosis of lymphedema was one of the factors used in determining sensitivity and specificity. If the differences in the timing of diagnosis were within 3 months, they were coded as an agreement. SAS version 8.2 was used for all statistical analyses.

Results

The patients eligible for inclusion in the study were African-American (30%), Caucasian (51.1%), Hispanic (3.3%), Arab/Chaldean (2.2%), Asian (2.2%), Native American (3.3%), and other (6.7%; Table 1). One subject did not indicate race (1.1%). Overall, the average age of the patients enrolled was 53.7 years, and all were women, although men were eligible to enroll as well. The evaluable subjects had breast cancer stages from 0 through IV. Forty-five of the patients (50%) had mastectomy with axillary surgery, 38 (42.2%) had lumpectomy with axillary surgery, and the remaining 7 (7.8%) had lumpectomy with radiation therapy. In addition, half of the patients had radiation therapy.

The patients were followed up in the trial for a mean of

Table 1
Patient characteristics

	With lymphedema	Without lymphedema
Number	38*	52
Mean age (yrs ± SD)	54.8 ± 13.4	54.4 ± 10.3
Race		
African American	14	13
Caucasian	16	30
Hispanic	3	0
Arab/Chaldean	1	1
Asian	0	2
Native American	0	3
Other	4	2
Unknown	0	1
Breast cancer stage		
0	3	6
I	7	17
IIA	11	11
IIB	5	14
IIIA	8	1
IIIB	3	2
IV	1	1
Chemotherapy	16	15
Radiation therapy	16	27
Employment status		
Working	15	28
Not working	10	7
Retired	10	8
Not answered	3	9
Highest education level		
Less than high school	4	1
High School/GED	21	28
Associate degree	0	0
Bachelor degree	8	9
Masters degree	1	4
Doctorate/professional school	1	1
Not available	3	9
Annual income		
<$5,000	3	4
$5,001–$15,000	6	4
$15,001–$30,000	5	5
$30,001–$50,000	3	2
$50,001–$75,000	3	8
>$75,000	10	13
Not available	8	16

* One patient had bilateral disease.

13 ± 7.9 months (range 3 to 36), with enrollment occurring throughout. Thirty-eight (38) patients (with 39 limbs affected) of the 90 evaluable patients (42.2%) were found to have lymphedema based on the academic trial standards of 10% increase in baseline volume or greater than 1 cm change at 1 of the 7 measured sites with verification by the lymphedema expert. One patient had bilateral disease. The mean age of patients with lymphedema was 54.8 years. Thirty-two of the 39 diagnoses (82.1%) of lymphedema were made within the first year (acute lymphedema). Most persisted past 1 year (86.7%). The average time until diagnosis of lymphedema was 7.6 months and ranged from 3 to 28 months (Table 2). There was no difference in incidence of lymphedema based upon type of surgical procedure.

Table 2
Lymphedema detection in academic trial by type of surgery*

	Type of breast cancer surgery			
	Mastectomy with axillary surgery (n = 45)	Lumpectomy with axillary surgery and RT (n = 38)	Lumpectomy and RT (n = 7)	All (n = 90)
With lymphedema	19	18	2	39‡
Acute LE†	13	18	2	33
Mean time to LE diagnosis (months)	8 ± 6	7 ± 6	6.5 ± 0.7	7.6 ± 5.8

* Academic trial LE criteria: 10% or greater volume change or 1 cm or greater circumference change at any site, all verified by LE specialist.
† Acute LE was lymphedema diagnosed within the first year after surgery.
‡ One patient had bilateral disease.
RT = radiation therapy; LE = lymphedema.

There were not enough cases of sentinel lymph node biopsy ([SLNB] 13) to compare these lymphedema criteria at this time. However, 5 of 13 were diagnosed with lymphedema in the academic trial after SNLB.

Based on one of the ACOSOG criteria for diagnosis of lymphedema, 10% change in circumference for measurements 10 cm above and below the elbow, 20 patients (37% sensitivity, 92% specificity) were identified. The average interval until diagnosis was 11.7 months (Table 3). When a 10% change in circumference was applied to any of the measurements along the limb, 29 patients (49% sensitivity, 81% specificity) were identified. The average interval until diagnosis was 10.7 months (Table 4).

Determining a greater than 2 cm change in circumference above and below the elbow identified 28 cases (59% sensitivity, 85% specificity) which overlapped with the cases identified by 10% circumference increase in the same sites (Table 5). Diagnosis of lymphedema occurred at 9.3 months on average. When all measured sites were examined for a greater than 2 cm change, then 32 cases were identified (70% sensitivity, 76% specificity; Table 5). The diagnosis occurred at 8.6 months on average.

In order to increase sensitivity, 5% changes in circum-

Table 3
Comparison of LE detection with the academic trial using 10% and 5% circumference change above and below the elbow

	10% change around elbow	5% change around elbow
Potential LE cases	18	45
Mean time to LE diagnosis (months)	11.7 ± 6.3	8.3 ± 5.9
Sensitivity	37%	80%
Specificity	92%	71%

LE = lymphedema.

Table 4
Comparison with the academic trial of LE detection using 10% and 5% circumference change at any site

	10% change at any site	5% change at any site
Potential LE cases	28	62*
Mean time to LE diagnosis (months)	10.7 ± 6.1	7 ± 5
Sensitivity	49%	91%
Specificity	81%	46%

* One patient had bilateral surgeries and was positive bilaterally.
LE = lymphedema.

ference were determined around the elbow (Table 3), and at all measured sites (Table 4). With a 5% circumference change around the elbow, there were 36 cases identified at a mean of 8.3 months (80% sensitivity, 71% specificity; Table 3). However, when 5% circumference change was determined for any measured site, then all 39 lymphedema cases from the academic trial were identified at 7.5 months (91% sensitivity, 46% specificity; Table 5).

Comments

Most patients do not have lymphedema after surgery or radiation therapy. However, for the approximately 30% of postsurgical/postradiation patients in whom the condition develops, it can be life altering and affect their quality of life. Interestingly, it can start within the first year after surgery. Some cases resolve within that year, others persist. Still others occur at some interval after the first year. There are several treatment modalities available for therapy. However, a delay in diagnosis delays therapy. Earlier treatment can prevent acute lymphedema from becoming more advanced and chronic, even if it does not resolve after 1 year. When it is left untreated, chronic lymphedema can progress to chronic inflammation, fibrosis, swelling, and increased risk of cellulitis [12]. Therefore, early identification of potential lymphedema remains a goal for surgical practices.

Table 5
Comparison with the academic trial of LE detection using >2 cm circumference change at any site and specifically above and below the elbow

	>2 cm around the elbow	>2 cm at any site
Potential LE cases	30	39
Mean time to LE diagnosis (months)	9.3 ± 6.2	8.6 ± 5.9
Sensitivity	59%	70%
Specificity	85%	76%

* One patient had bilateral disease.
LE = lymphedema.

The diagnosis is more complex in patients who experience a feeling of heaviness, swelling, or pain, in the absence of corroborating volume or circumferential changes. These patients may be considered to have lymphedema by subjective complaints and require evaluation a by lymphedema specialist as well [13]. The subjective complaints often times precede the ability to clinically document lymphedema [9]. The physical changes that accompany the condition create difficulty with tasks associated with jobs, households, and even personal care, especially in severe cases [14]. The psychological impact can be tremendous resulting in sexual dysfunction, depression, and feelings of isolation.

Modern day surgical practices in breast surgery are aimed at reducing post surgical and treatment morbidity. With the advent of SNLB, it has been reported that arm swelling and subjective complaints are decreased in comparison with traditional axillary lymph node dissection (ALND) [15–17]. Sener et al [17] reported 6.9% incidence of lymphedema in patients undergoing SLNB followed by obligatory ALND. The incidence of lymphedema decreased to 3% with SNLB alone (lymphedema was characterized by a minimum 20% volume change in that particular study). Although the data are promising, the number of lymphedema cases was falsely low due to the determination of a greater than 20% circumference increase at sites 10 cm above and below the elbow. This is predicted to increase the false negative rate for lymphedema detection. Therefore, future studies examining the occurrence of lymphedema in cases with SLNB require standardized criteria for identifying potential cases.

Although there are generally accepted criteria to diagnose lymphedema, there are no universally applied methods to diagnose potential lymphedema, thereby complicating interpretation of literature. This also has serious implications for surgical practice in making a presumptive diagnosis and referral to a lymphedema specialist. While a lymphedema specialist may apply multiple complex measurements and other clinical evaluations in arriving at the confirmation of lymphedema, surgeons may need simpler screening criteria that would reliably detect lymphedema in order to refer for consultation. For example, some authors have used or referred to a method of two measurements (one above and one below the elbow) with a 2 cm increase in circumference for diagnosis of lymphedema [2,4,15,18], When data from the subjects in this study was evaluated by this criterion, we found that 28 of the 39 (71.8%) cases diagnosed with lymphedema would also have been diagnosed by this method (Table 5). When the 2 cm increase was applied to any site, the true positive diagnosis rate was 82.1%, missing 17.9% of the cases.

When ACOSOG criteria for lymphedema were applied to the measurement data (10% increase in circumference around elbow), 48.7% of the documented lymphedema cases would have been missed as compared with evaluating sites along the arm (Table 3). Ten cases (25.6%) would have been missed based on the ACOSOG criteria of 10% cir-

cumferential change if applied to any site. In addition, the academic trial identified patients with lymphedema 3 months earlier on average in comparison to ACOSOG criteria. It should be noted, however, that if the ACOSOG criteria of 10% change over baseline measurement was lowered to 5%, all of the patients identified by the academic trial would have been positively diagnosed with lymphedema by that standard (Tables 3 and 4). On average, patients would have been diagnosed 3.7 months earlier if this criterion were utilized instead of 10% and 0.6 month earlier than using a 10% volume change.

In addition, we used a greater than 1 cm change in circumference at any site as a trigger for referral to the lymphedema specialist who would further evaluate for lymphedema [3,19,20]. Thirty-seven of 39 lymphedema cases had a greater than 1 cm change. We feel that this is a reliable indicator of lymphedema. However, although the sensitivity was 76% for this approach, the specificity was only 39%. This may lead to a greater number of referrals to the lymphedema specialist than would have the diagnosis. With confirmation of the diagnosis, lymphedema therapy could begin.

In conclusion, methods of lymphedema diagnosis that are readily available, inexpensive, quantifiable, and easily reproduced are ideal for evaluation of patient in a surgical practice [6]. The academic trial utilizing frequent measurements and volumetric determinations identified lymphedema in 43.3% of the total patients evaluated, which is higher than the general incidence of lymphedema reported in the literature [2]. The methodology is also more complex than would be practical in a surgical practice. However, simpler determination of circumference change at multiple sites along the affected limb may identify potential cases for referral, leading to earlier treatment and lessen the psychosocial and physical impact. By using a 5%, rather than 10% change in circumference or using a greater than 1 cm change in measurement at sites along the length of the arm, reliable detection of probable lymphedema in a clinical setting can be accomplished without complicated volume determination. The later can be utilized by lymphedema specialists along with other complex evaluations.

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